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Letter to the Editor

Osteocraniostenosis vs. Severe Hallermann-Streiff-François Syndrome

To the Editor:

In 1994, we suggested the existence of a "new" lethal bone dysplasia we named osteocraniostenosis [Verloes et al., 1994]. The skeletal anomalies consisted of extremely thin, dense, easily fractured, and misshapen fishbone-like diaphyses with almost absent medullary lucency, flared metaphyses ("drumstick-shape bones"), mild micromelic dwarfism of intrauterine onset, poorly mineralised cranial vault with premature synostoses, platyspondyly, and brachydactyly. It was observed in 3 unrelated fetuses. Those babies also had a flat face, hypoplastic midface with short or flat, but not a narrow nose, deep nasal root, inverted V-shape mouth, and acrocephalic head with bulging frontal and parietal areas, compatible with a cloverleaf skull deformity. Pathological investigations showed abnormalities of the metaphyseal cartilage in the 2 fetuses we could examine and epiphyseal dysplasia in one of them. We considered 3 previously reported cases published in 2 heterogeneous series of fetuses with slim bones and intrauterine fractures (case 1 and 3 in Kozlowski and Kan [1988] and case 6 in Maroteaux et al. [1988]) as affected by the same MCA syndrome. We excluded the diagnosis of Hallermann-Streiff-François syndrome (HSF) in our cases, considering the absence of characteristic facial changes and the presence of distinctive X-ray anomalies.

In a recent report of this journal, Dennis et al. [1995] described 2 sibs with a pattern of anomalies strikingly similar to that of our cases. They did not mention our article in their discussion, nor Maroteaux's work, but as we did, they noted similarities with case 1 in Kozlowski's report. They based their diagnosis and discussion on a review of radiological aspects in HSF syndrome [Christian et al., 1991] describing 5 cases of HSF, 2 of them (cases 1 and 2) with drumstick-shape long bones. Patient 2 in that article had X-ray findings similar to those of our cases and died of heart failure of unknown etiology at age 1 month. Patient 1 showed similar long bone X-ray findings (although with a milder metaphyseal flare), no fractures. Hands were not illustrated, and she was lost to follow-up. Unfortunately, those 2 children were not illustrated. Considering the similarities with Christian's cases 1 and 2, Dennis suggested a diagnosis of severe HSF for his cases.

I do not share this opinion. For me, the 10 patients considered here, and summarised in Table I, suffer from a radiologically identical disorder and for those where clinical pictures are available, share a similar phenotype, which I feel is atypical of HSF (Dennis' case 1 being the less atypical, I agree). In most circumstances, HSF is a nonlethal MCA syndrome with a very particular morphogenetic Gestalt that usually allows immediate pattern recognition [François, 1982; Cohen, 1991]. Although ocular anomalies and some facial traits are similar in HSF and osteocraniostenosis, we did not observe in the latter the typical thin, tapering, beaked, and pinched nose with slit-shape nares, nor the impressive short mandible that is usually already present at birth in HSF. Neither pathological fractures, bowed forearms, nor disproportionate shortness of limbs are typical of HSF, and platyspondyly is rarely mentioned; it was noted in François [1958] and patient 5 of Christian et al. [1991]. In typical HSF cases, long bones are more uniformly thin and straight and the metaphyses are not so disproportionately flared, as illustrated, for instance, at age 18 days, in patient 2 of Kurlander et al. [1966]. In osteocraniostenosis, the medullar axis of the diaphyses is almost invisible on X-ray films. The appearance of the hands, with short, tapering fingers, small to hypoplastic nails, distal phalanx hypoplasia, and short metacarpal I, seems one of the most important findings to distinguish osteocraniostenosis from HSF. For those reasons, we suggest that Dennis' cases and at least case 2 of Christian (and probably case 1 either) do not have "classical" HSF but rather the syndrome we described as osteocraniostenosis.

Following Cohen's [1991] opinion, no convincing familial HSF has been published. With the exception of concordant monozygotic twins, all "true" HSF cases (which are >150 in number) were sporadic (thus favouring fresh dominant mutation). A possible recurrence in sibs born of consanguineous parents [Bueno-Sanchez, 1966] could be an exception. This latter case and the unverified affirmations of François [1982] about familial cases and frequent consanguinity in parents seem to have been the justification for allocating HSF to the recessive section of MIM (#234100). If a dominant mutation is responsible for HSF, gonadal mosaicism probably is a rare event in HSF.

Of course, there is no objective means to demonstrate that osteocraniostenosis and HSF are causally different entities with overlapping manifestations rather

Correspondence to: Alain Verloes, Centre for Human Genetics, CHU Sart Tilman, B-4000 Liège, Belgium.

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TABLE 1. Comparison of Classical Hallermann-Streiff-François Syndrome and 10 Cases of Osteocraniostenosis

		Verloes et al.			Maroteaux et al.	Kozlowski & Kan		Christian et al.		Dennis et al.	
Case #	Typical HSF	1	2	3	6	1	3	1	2	1	2
Sex		F	M	F	?	M	?	F	F	F	F
Paternal age		31	?	?	?	?	?	?	?	30	
Maternal age		24	29	?	?	?	?	?	16	30	
Gestation		24	32	37	33	32	?	NB	36	35	29
Short stature	Y (45–68%)	Y	N	N	Y	Y	?		?	N	N
Frontal bossing	Y (32%)	YY	Y	Y	?	Y	?	?	?	Y	Y
Temporoparietal bossing	Y (8%)	YY	Y	Y	?	Y	?	Y	?	Y	Y
Vault hypomineralisation	Y	Y	Y	Y	Y	?	?	Y	Y	Y	Y
Abnormal nose	Thin, tapering (24%), pinched and beaked (45%)	Short, wide and upturned	Prominent, with deep root	Wide, flat	?	Large	?	Prominent nasal bone	Prominent nasal bone	Prominent beaked and narrow	Prominent beaked
Malar/midface hypoplasia	Y	Y	Y	N	?	?	?	Y	Y	Y	Y
Short philtrum	N	Y	Y	Y	?	Y	?	?	?	Y	Y
Down-turned mouth	Secondary to the micrognathia	Y	Y	Y	?	Y	?	?	?	Y	Y
Microstomia	Y (10%)	Y	Y	Y	?	Y	?	?	?	Y	Y
Micrognathia	Y	N	N	N	?	?	?	?	?	Y? (open mouth)	N
Low set, posteriorly rotated ears	N	Y	Y	Y	?	?	?	?	?	Y	Y
Disproportionate micromelia	N	Y	Y	Y	Y	Y	?	?	Y?	Y	Y
Acromicry/ brachydactyly	N	Y	Y	Y	?	Y	?	?	Y	Y	Y
Gracile diaphyses	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Drumstick long bones	Absent to mild	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Drumstick phalanxes	N	Y	Y	Y	Y	Y	?	?	Y	Y	Y
Bowed forearms	N	Y	Y	Y	?	?	?	Y	Y	?	Y
Platyspondyly	N (rare)	Y	Y	?	Y	N	?	Y	Y	Y	Y
Fracture	N	Y	Y	N	YY	YY	YYY	N	YY	YY	Y
Ocular anomaly	Y	Microphthalmia + aniridia	?	?	?	?	?	?	Microphthalmia + sclerocornea	Microphthalmia and cataracts	?
Spleen hypo/aplasia	?	Y	Y	Y	?	?	?	?	N	N	?
Abnormal metaphyseal histology	?	Y	N	?	?	N	?	?	N	Y	?
Abnormal epiphyseal histology	?	Y	Y	?	?	N	?	?	N	N	?

than variable (allelic ?) expressions of a single genetic defect. Because HSF is sporadic, the natural variations of its spectrum cannot be established by studying its manifestations in related cases of the typical propositi, which means that unusually mild or severe HSF, or "variant forms" could not be recognised as such as long as the aetiology of the syndrome remains *in limbo* (similar discussion was already published about the overlap of HSF and oculodentodigital dysplasia) [Kurlander et al., 1966; Spaepen et al., 1991]. Two out of 10 cases of osteocraniostenosis (in my sense) occurred in sibs. This is a strong (but not definitive) argument for autosomal recessive inheritance of osteocraniostenosis and another argument for its distinction from HSF. New cases and longitudinal X-ray surveys of typical HSF and osteocraniostenosis would be of major importance in sorting out the nosology of the two MCA syndromes discussed here.

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Alain Verloes
Centre for Human Genetics
CHU Sart Tilman
Liège, Belgium